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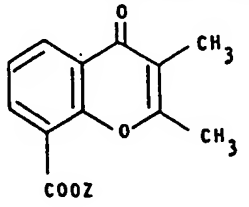
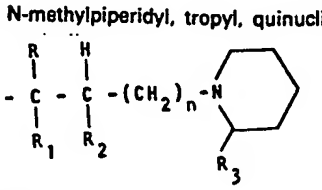
(54) **3-Methylflavone-8-carboxylic acid esters.**

(57) 3-Methylflavone-8-carboxylic acid esters I are provided. They may be prepared by condensing a 3-methylflavone-8-carboxylic acid halide (preferably the chloride with an aminoalcohol ZOH. Condensation conditions are (a) no solvent, 140-200°C, excess flavone derivative or (b) organic solvent, 0°C to reflux, equimolar reactant proportions, hydrogen halide acceptor optional. The esters have muscle relaxant and calcium blocking action. They are also anaesthetics and anti-inflammatory agents.



(1)

Z = N-methylpiperidyl, tropyl, quinuclidyl or



(11)

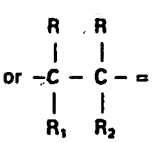
n = 0,1

R = H,Ph,C_1-C_4 alkyl

R_1 = H,C_1-C_4 alkyl

R_2 = H, OH

R_3 = H, C_1-C_4 alkyl

or  = C_4-C_6 cycloalkyl

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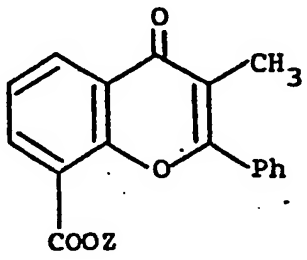
TITLE:

3-Methylflavone-8-carboxylic acid esters

DESCRIPTION:

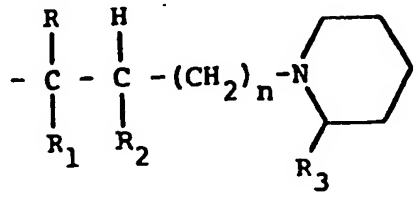
The invention relates to esters of 3-methylflavone-8--carboxylic acid, to pharmaceutically acceptable salts thereof, to processes for the preparation of the esters and their salts, and to pharmaceutical compositions containing the esters or their salts. It is known that certain esters of 3-methylflavone-8-carboxylic acid exhibit a good spasmolytic activity (see United States Patent Specification No. 2,921,070). Their action, however, might be improved by increasing their stability at physiological pH.

The invention provides 3-methylflavone-8-carboxylic acid esters having the general formula I



(I)

wherein Z represents an N-methylpiperidyl, tropyl or quinuclidyl group or a group of the general formula II

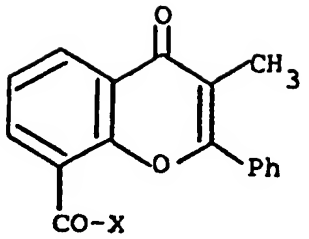


(II)

in which n is 0 or 1, R represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a phenyl group, R_1 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, R_2 represents a hydrogen atom or a hydroxy group, or R, R_1 and R_2 together with the carbon atoms to which they are attached represent a cycloalkyl ring having from 4 to 6 carbon atoms, and R_3 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, and further provides pharmaceutically acceptable salts of such esters.

The compounds according to the invention have been found to exhibit powerful smooth muscle relaxant, calcium blocking, local anaesthetic, and anti-inflammatory properties. They are considerably stable at the physiological pH, so that the half-life of the drug is highly prolonged. It has been found moreover, that the novel esters possess further activities whereas their toxicity is diminished or, at most, unaltered when compared with the known compounds.

The invention further provides a process for the preparation of the compounds having the general formula I as above defined, the process comprising condensing a 3-methylflavone-8-carboxylic acid halide having the general formula III



(III)

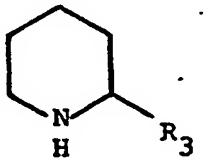
wherein X represents a halogen atom with an aminoalcohol of the general formula ZOH, wherein Z is as above defined.

The 3-methylflavone-8-carboxylic acid halide is preferably 3-methylflavone-8-carboxylic acid chloride (III, X=Cl), and is a known compound (see United States Patent Specification No. 2921070). It is readily prepared by reacting the corresponding acid with thionyl chloride or phosphorus trichloride. The acid is prepared according to the standard procedures for the manufacturing of flavones.

The condensation may be carried out in the presence or absence of a solvent. If carried out in the absence of a solvent, the reactants are heated together at a temperature of from 140°C to 200°C, and an excess of the 3-methyl-flavone-8-carboxylic acid is employed. If carried out in the presence of a solvent, the reactants are generally used in equimolar proportions, the temperature may be from 0°C to the reflux temperature of the solvent, and an acid-binding agent (hydrogen halide acceptor) may optionally be present. Suitable solvents include all inert inorganic solvents, particularly dimethylformamide, ethers and halogenated hydrocarbons. Aromatic hydrocarbons, such

as benzene and toluene, are also useful, especially when the reaction is carried out at reflux temperature. The acid-binding agent may be any of those customarily used in such condensations, for example, organic bases such as triethylamine and inorganic bases such as alkali metal hydroxides and alkali metal carbonates.

The invention also provides a further process for the preparation of the compounds having the general formula I in which Z represents a group of the general formula II wherein n is 1, R and R_1 both represent hydrogen atoms and R_2 represents a hydroxy group. This further process comprises reacting a compound of the general formula IV



(IV)

wherein R_3 is as above defined with 2,3-epoxypropyl 3--methylflavone-8-carboxylate in the presence of a catalyst. The 2,3-epoxypropyl 3-methylflavone-8-carboxylate is a novel compound, but can be prepared by condensing a 3--methylflavone-8-carboxylic acid halide (preferably the chloride) with 2,3-epoxy-1-propanol. The reaction may be carried out in the presence of an organic solvent, such as any of those previously mentioned or a nitrile such as acetonitrile. The catalyst may be an organic base such as triethylamine.

Generally equimolar amounts of reactants are employed, and

the temperature ranges from 20 to 80°C. The reaction is preferably carried out at 40-60°C.

The salts according to the invention may be prepared from the basic esters obtained by the processes described above according to conventional methods such as addition of an acid to the free base dissolved in a suitable solvent. Suitable acids include hydrogen halides, phosphoric acid, nitric acid, alkylsulphonic acids, arylsulphonic acids, monofunctional and bifunctional carboxylic acids, hydroxy--carboxylic acids and 1,5-naphthalenedisulphonic acid. Isolation and purification may be effected conventionally.

The invention additionally provides a pharmaceutical composition comprising a compound having the general formula I as above defined or a pharmaceutically acceptable salt thereof in admixture with a pharmaceutically acceptable diluent or carrier.

The active compounds according to the invention exhibit a powerful smooth muscle relaxant and a calcium blocking action. They are also good anaesthetic and anti-inflammatory agents. As stated above, their stability at physiological pH is, however, the most interesting factor when compared with similar flavone derivatives.
The stability was studied at 37°C in gastric fluid simulated (U.S.P. XX, 1105, 1980) and in phosphate buffer (pH 7.4) by spectrodensitometric determination of 3-methylflavone-

-8-carboxylic acid resulting from eventual hydrolysis. As comparison substance 2-piperidino-ethyl 3-methylflavone-8--carboxylate hydrochloride (Flavoxate) was selected, this being the best of the esters disclosed in our United States Patent Specification No. 2,021,070.

The results are reported in Table I. In this Table, and in subsequent Tables, the numbers identifying the active compounds are those assigned to the respective active compounds in the Examples which follow and which describe their preparation.

TABLE I

Stability test, pH 7.4

Active compound	1 hour	3 hours
1	100	100
2	100	100
3	40	30
4	68	34
5	96	91
6	100	100
7	44	25
8	85	70
9	88	87
10	100	100
11	100	100
12	100	100
13	100	100
FLAVOXATE	22	10

The LD_{50} of the new esters was determined in mice both i.p. and per os, following the method described by C.S. Weil (Biometrics, 8, 249, 1952). The results obtained are reported in Table II.

TABLE II

Active compound	LD_{50} mM/Kg i.p.	os
1	0.56	1.86
2	0.16	0.69
3	0.5	0.85
7	0.58	3.10
8	--	2.16
9	0.19	1.08
10	0.15	0.85
11	0.36	0.77
12	0.42	0.95
13	0.12	0.50
FLAVOXATE	0.90	1.89

The calcium blocking activity was tested on guinea pig depolarized taenia coli, according to the method described by Ferrari and Carpenedo (Arch.Int.Pharmacodyn., 174, 223, 1968). The guinea pig taenia coli was allowed to stabilize in Tyrode solution without Ca^{++}. It was then washed with K_2SO_4 Ringer solution and afterwards perfused with KNO_3

Ringer. Cumulative concentrations of $CaCl_2$ were added to the organ bath in absence or presence of the drug to test. The obtained results are reported in Table III.

TABLE III

Calcium blocking activity

Active compound	ED_{50} (μM)
1	24
2	16
3	19
5	8.6
6	7.5
8	7.3
9	26
FLAVOXATE	25

The antispastic activity was evaluated following the Magnus method (Pflügers Arch.Gen.Physiol., 102, 123, 1904). Two equal contractions were induced by $BaCl_2$ at a concentration ranging between 1 and 4.10^{-4} M in guinea pig ileum maintained at 30°C in Ringer solution and aerated with Carbogen.

The drug to test was administered and, a minute later, $BaCl_2$ to the same concentration. The inhibition of the contraction was observed. The results are given in Table IV.

TABLE IV

Active Compound	ED_{50} (μM)
1	4
2	6.2
3	9.7
4	6.7
5	2.4
6	3.4
8	2.7
9	4
12	4.3
13	2.1
14	7.7
FLAVOXATE	5.6

The smooth muscle relaxant activity of the novel flavone derivatives has been also studied through the spontaneous mobility of guinea pig isolated ureter. The test has been executed according to the Trendelemburg method (Arch.Exp.Path.Pharmak., 81, 55, 1917). The ureter was allowed to stabilize in Tyrode solution with the upper part closed and the inner part connected to a pressure transducer. The drugs to test were given in a cumulative way and the spontaneous circular and longitudinal

contractions of the ureter were measured. The results obtained are listed in Table V.

TABLE V

Antispastic activity Isolated ureter (ED_{50}, μM)

Active compound	circular contractions	longitudinal contractions
1	8.5	6.9
5	12	2.8
6	5.3	2.5
8	5	2.5
12	20	9

The following Examples illustrate the invention.

EXAMPLE 1

To a mixture consisting of 7.86 g of 3-(2-methylpiperidino)--propanol, 40 ml of anhydrous dimethylformamide and 10.5 g of anhydrous potassium carbonate, 14.9 g of 3-methylflavone-8-carboxylic acid chloride were added. The mixture was heated at 60°C for 8 hours under stirring then it was poured in 500 ml of icy water. The precipitate thus formed was extracted with diethyl ether, washed with water and dried. The solvent was evaporated off and the compound, as brown oil residue, was transformed into the corresponding hydrochloride (1) by adding hydrogen chloride in isopropanol. The 3-(2-methylpiperidino)-propyl 3-methylflavone-8-carboxylate hydrochloride melts at 185-187°C.

EXAMPLE 2

To a stirred suspension consisting of 5.75 g of 3--hydroxy-N-methylpiperidine and 10.4 g of anhydrous potassium carbonate in 50 ml dimethylformamide, 14.9 g of 3-methylflavone-8-carboxylic acid chloride were added. The mixture was stirred at ambient temperature for 20 hours, poured into icy water and the precipitate thus formed was extracted with ethyl acetate. The extract was neutralized with water and dried. The solvent was evaporated off and the residue was dissolved in isopropanol. After cooling, hydrogen chloride in isopropanol was added. The hydrochloride (11) was washed with diethyl ether and crystallized from isopropanol. The desired N-methyl-3-piperidyl 3-methylflavone-8--carboxylate hydrochloride melts at 228-229°C. The free base was crystallized from hexane, mp 90-93°C.

EXAMPLE 3

To a stirred mixture, cooled at 10-15°C, and consisting of 12.8 g of 3-hydroxyquinuclidine, 240 ml of dimethylformamide and 20 g of triethylamine, were added in 30-40 minutes 29.8 g of 3-methylflavone-8-carboxylic acid chloride. The temperature was allowed to reach 20-25°C, the mixture was stirred for 4 hours and then poured into icy water. The precipitate thus formed was separated, washed with water and then extracted with ethyl acetate. The extract was washed with aqueous sodium carbonate solution, then with water and dried. The residue was chromatographed on a

silica gel column using ethyl acetate : methanol (7:3 by volume) and chloroform : methanol (87:13 by volume) as eluent. 11.25 g of the desired compound, mp 180-181°C, were obtained. The free base was transformed into the corresponding hydrochloride (13) by adding hydrogen chloride in ethanol. The 3-quinuclidyl 3-methylflavone--8-carboxylate hydrochloride was crystallied from ethanol, mp 302-305°C.

EXAMPLE 4

To a solution of 4.6 g of cis-2-piperidino-cyclohexanol in 100 ml of anhydrous benzene, stirred and maintained at 20-25°C, 7.5 g of 3-methylflavone-8-carboxylic acid chloride were added over a period of 15 minutes. The mixture was refluxed for 18 hours, then cooled to ambient temperature. The product thus formed was filtered off, washed with ethyl acetate, dried, and crystallized from ethanol. The cis-2-piperidino-cyclohexyl 3-methylflavone-8-carboxylate hydrochloride (8) melts at 258-259°C. The trans form (14) was similarly obtained by starting from trans-2-piperidino-cyclohexanol. Its hydrochloride melts at 222-225°C. Using 1,1-dimethyl-2-piperidino--ethanol instead of cis-2-piperidino-cyclohexanol, 1,1--dimethyl-2-piperidino-ethyl 3-methylflavone-8-carboxylate was prepared. The compound was directed isolated as its hydrochloride (5) of melting point 203-207°C.

From this salt the free base was separated. It melted at 103-105°C. Moreover, the following salts have been prepared:

Nitrate	mp. 179°C (with decomposition)
Sulphate	mp. 208°C (with decomposition)
Phosphate	mp. 175-176°C (with decomposition)
Maleate	mp. 144-148°C
p-Toluenesulphonate	mp. 149-152°C

Using 1,1-dimethyl-2-(2-methylpiperidino)-ethanol instead of cis-2-piperidino-cyclohexanol, 1,1-dimethyl--2-(2-methyl-piperidino)-ethyl 3-methylflavone-8--carboxylate (6) was obtained. This compound, as hydrochloride, melts at 194-195°C.

The free base was separated from this salt, and had a melting point of 78-80°C. The following salts were also prepared:

Hydrobromide	mp. 209°C
Nitrate	mp. 170°C (with decomposition)
Sulphate	mp. 184-188°C
Maleate	mp. 147-149°C
p-Toluenesulphonate	mp. 157-159°C

EXAMPLE 5

A mixture comprising 8.9 g of tropine hydrochloride and 22.5 g of 3-methylflavone-8-carboxylic acid chloride was heated for 4 hours at 170-175°C under a nitrogen atmosphere. When the reaction was over, a further 7.5 g of the flavone derivative were added and the mixture was heated again for 11 hours at the same temperature. After cooling, the product was powdered, suspended in water and stirred for 6 hours. The whole was filtered off and dilute sodium hydroxide solution was added to the solution. The precipitate was centrifuged, washed with water and dried. The desired compound, tropyl 3-methyl-flavone-8-carboxylate, was treated with hydrogen chloride in ethanol to give the corresponding hydrochloride (12), melting point 276-278°C.

EXAMPLE 6

21.3 g of 3-methylflavone-8-carboxylic acid chloride were slowly added, over a period of 4 hours at 20°C, to a stirred solution of 5.55 g of 2,3-epoxy-1-propanol and 8.34 g of triethylamine in 165 ml of anhydrous benzene. The mixture was allowed to stand at 20-25°C for 20 hours, and then 60 ml of water were added. The whole was stirred for 15 minutes and the layers were separated. The organic

layer was washed and dried, the solvent was evaporated off and 18.95 g of 2,3-epoxypropyl 3-methylflavone-8--carboxylate, m.p. 103-105°C, was obtained.

A mixture comprising 16.8 g of the 2,3-epoxypropyl 3--methylflavone-8-carboxylate, 100 ml of acetonitrile, 5.5 ml of piperidine and 7 ml of triethylamine was heated at 60°C for 12 hours. The solvent was evaporated off and the brown, oily residue was washed twice with 75 ml of benzene. The 2-hydroxy-3-piperidino-propyl 3-methyl-flavone-8-carboxylate thus formed was converted into the corresponding hydrochloride (7) in the usual manner. Mp 187-189°C.

EXAMPLE 7

Following the procedure described in Example 2, the following esters of 3-methylflavone-8-carboxylic acid were prepared from appropriate starting materials:

(2) 1-methyl-3-piperidino-propyl, separated as its hydrochloride hemihydrate, mp 161-168°C;

(10) 1-methyl-4-piperidyl, melting at 103-105°C;

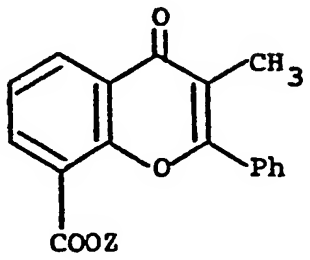
(3) 1-methyl-2-piperidino-ethyl, separated as its hydrochloride hydrate, mp 218-220°C;

(4) 1-phenyl-2-piperidino-ethyl (hydrochloride) of melting point 219-221°C; and

(9) 2-piperidinomethyl cyclohexyl, as hydrochloride, mp 236-237°C.

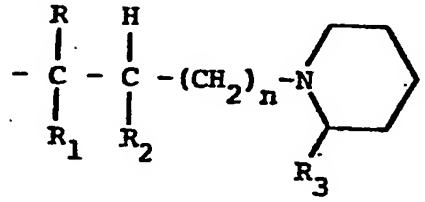
CLAIMS:

1. A 3-methylflavone-8-carboxylic acid ester having the general formula I



(I)

wherein Z represents an N-methylpiperidyl, tropyl or quinuclidyl group or a group of the general formula II



(II)

in which n is 0 or 1, R represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a phenyl group, R_1 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, R_2 represents a hydrogen atom or a hydroxy group, or R, R_1 and R_2 together with the carbon atoms to which they are attached represent a cycloalkyl ring having from 4 to 6 carbon atoms, and R_3 represents a hydrogen atom or an alkyl group having from 1 to 4

carbon atoms; or a pharmaceutically acceptable salt of such an ester.

2. 3-(2-Methylpiperidino)-propyl 3-methylflavone-8-carboxylate.

3. N-Methyl-3-piperidyl 3-methylflavone-8-carboxylate.

4. 3-Quinuclidyl 3-methylflavone-8-carboxylate.

5. cis-2-Piperidino-cyclohexyl 3-methylflavone-8--carboxylate.

6. trans-2-Piperidino-cyclohexyl 3-methylflavone-8--carboxylate.

7. 1,1-Dimethyl-2-piperidino-ethyl 3-methylflavone--8-carboxylate.

8. 1,1-Dimethyl-2-(2-methylpiperidino)-ethyl 3--methylflavone-8-carboxylate.

9. Tropyl 3-methylflavone-8-carboxylate.

10. 2-Hydroxy-3-piperidinopropyl 3-methylflavone-8--carboxylate.

11. 1-Methyl-3-piperidino-propyl 3-methylflavone-8--carboxylate.

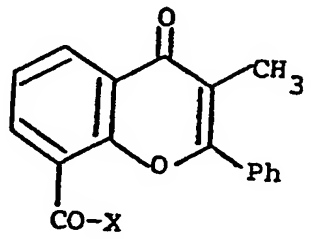
12. 1-Methyl-4-piperidyl 3-methylflavone-8-carboxylate.

13. 1-Methyl-2-piperidino-ethyl 3-methylflavone-8--carboxylate.

14. 1-Phenyl-2-piperidino-ethyl 3-methylflavone-8--carboxylate.

15. 2-Piperidinomethyl-cyclohexyl 3-methylflavone-8--carboxylate.

16. A process for the preparation of a compound according to claim 1, the process comprising condensing a 3-methylflavone-8-carboxylic acid halide having the general formula III



(III)

wherein X represents a halogen atom with an amino-alcohol of the general formula ZOH wherein Z is as above defined.

17. A process according to claim 16 in which X represents a chlorine atom.

18. A process according to claim 16 or claim 17 carried out by heating the aminoalcohol with an excess of the flavone derivative at from 140°C to 200°C in the absence of a solvent.

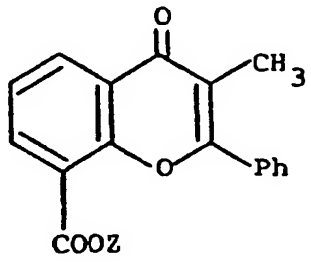
19. A process according to claim 16 or claim 17 carried out by reacting the aminoalcohol with an equimolar amount of the flavone derivative in the presence of a solvent at a temperature of from 0°C to

the reflux temperature of the solvent.

20. A process for the preparation of a compound according to claim 1, the process being substantially as described herein with reference to any of Examples 1 to 5 or 7.

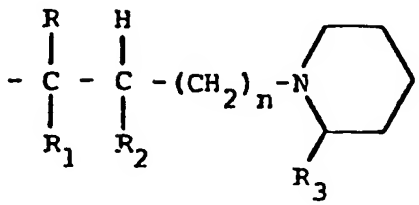
21. A process according to claim 19 carried out in the presence of an acid-binding agent.

22. A process for the preparation of a 3-methyl-flavone-8-carboxylic acid having the general formula I



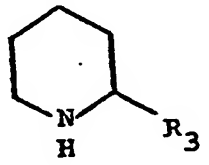
(I)

wherein Z represents a group of the general formula II



(II)

wherein n is 1, R and R_1 both represent hydrogen atoms, R_2 represents a hydroxy group and R_3 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, the process comprising reacting a compound of the general formula IV



(IV)

wherein R_3 is as above defined with 2,3-epoxypropyl 3-methylflavone-8-carboxylate in the presence of a catalyst.

23. A process according to claim 22 in which the catalyst is triethylamine.

24. A process according to claim 23 carried out in a solvent at from 20°C to 80°C using equimolar proportions of the flavone and piperidine derivatives.

25. A process for the preparation of a 3-methyl-

flavone-8-carboxylic acid having the general formula I as defined in claim 22, the process being substantially as described herein with reference to Example 6.

26. A pharmaceutical composition comprising a 3-methylflavone-8-carboxylic acid ester according to claim 1 or a pharmaceutically acceptable salt of such an ester in admixture with a pharmaceutically acceptable diluent or carrier.

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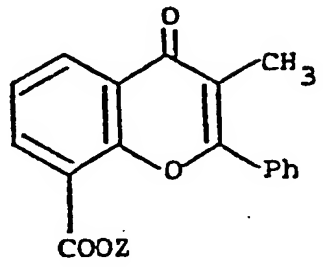
Amended Claims

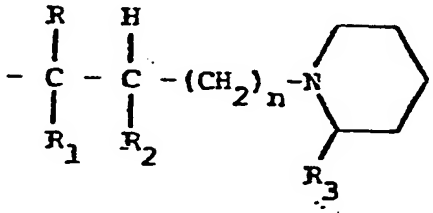
CLAIMS:

1. A 3-methylflavone-8-carboxylic acid ester having the general formula I



(I)

wherein Z represents an N-methylpiperidyl, tropyl or quinuclidyl group or a group of the general formula II



(II)

in which n is 0 or 1, R represents a hydrogen atom, an alkyl group having from 1 to 4 carbon atoms or a phenyl group, R_1 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, R_2 represents a hydrogen atom or a hydroxy group, or R, R_1 and R_2 together with the carbon atoms to which they are attached represent a cycloalkyl ring having from 4 to 6 carbon atoms, and R_3 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, with the proviso that R, R_1, R_2 and R_3 do not all simultaneously represent hydrogen

Amended claims

atoms; or a pharmaceutically acceptable salt of such an ester.

2. 3-(2-Methylpiperidino)-propyl 3-methylflavone-8-carboxylate.

3. N-Methyl-3-piperidyl 3-methylflavone-8-carboxylate.

4. 3-Quinuclidyl 3-methylflavone-8-carboxylate.

5. cis-2-Piperidino-cyclohexyl 3-methylflavone-8--carboxylate.

6. trans-2-Piperidino-cyclohexyl 3-methylflavone-8--carboxylate.

7. 1,1-Dimethyl-2-piperidino-ethyl 3-methylflavone--8-carboxylate.

8. 1,1-Dimethyl-2-(2-methylpiperidino)-ethyl 3--methylflavone-8-carboxylate.

9. Tropyl 3-methylflavone-8-carboxylate.

10. 2-Hydroxy-3-piperidinopropyl 3-methylflavone-8--carboxylate.

11. 1-Methyl-3-piperidino-propyl 3-methylflavone-8--carboxylate.

12. 1-Methyl-4-piperidyl 3-methylflavone-8-carboxylate.

13. 1-Methyl-2-piperidino-ethyl 3-methylflavone-8--carboxylate.

14. 1-Phenyl-2-piperidino-ethyl 3-methylflavone-8--carboxylate.

15. 2-Piperidinomethyl-cyclohexyl 3-methylflavone-8--carboxylate.

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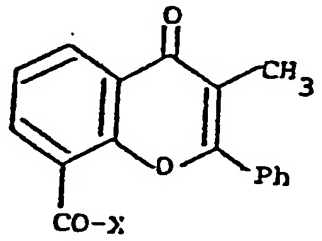
Claims

16. A process for the preparation of a compound according to claim 1, the process comprising condensing a 3-methylflavone-8-carboxylic acid halide having the general formula III



(III)

wherein X represents a halogen atom with an amino-alcohol of the general formula ZOH wherein Z is as defined in claim 1.

17. A process according to claim 16 in which X represents a chlorine atom.

18. A process according to claim 16 or claim 17 carried out by heating the aminoalcohol with an excess of the flavone derivative at from 140°C to 200°C in the absence of a solvent.

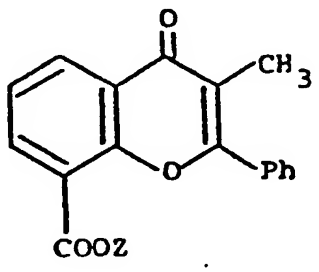
19. A process according to claim 16 or claim 17 carried out by reacting the aminoalcohol with an equimolar amount of the flavone derivative in the presence of a solvent at a temperature of from 0°C to

 Amended Claims 0072620

the reflux temperature of the solvent.

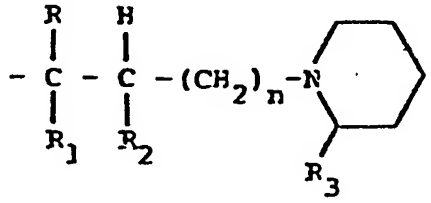
20. A process according to claim 19 carried out in the presence of an acid-binding agent.

21. A process for the preparation of a 3-methyl--flavone-8-carboxylic acid having the general formula I



(I)

wherein Z represents a group of the general formula II

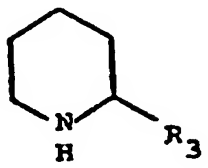


(II)

wherein n is 1, R and R_1 both represent hydrogen atoms, R_2 represents a hydroxy group and R_3 represents a hydrogen atom or an alkyl group having from 1 to 4 carbon atoms, the process comprising

Amended Claims

reacting a compound of the general formula IV



(IV)

wherein R_3 is as defined in claim 1 with 2,3-epoxypropyl 3-methylflavone-8-carboxylate in the presence of a catalyst.

22. A process according to claim 21 in which the catalyst is triethylamine.

23. A process according to claim 22 carried out in a solvent at from 20°C to 80°C using equimolar proportions of the flavone and piperidine derivatives.

24. A pharmaceutical composition comprising a 3-methylflavone-8-carboxylic acid ester according to claim 1 or a pharmaceutically acceptable salt of such an ester in admixture with a pharmaceutically acceptable diluent or carrier.

European Patent Office

EUROPEAN SEARCH REPORT

Application number
0072620

EP 82303634.8

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim
D,A	US - A - 2 921 070 (DA RE) * Column 1, lines 1-53; column 2, lines 12-19 * --	1,16, 19,21
A	US - A - 4 217 351 (DREN) * Abstract * ----	1

CLASSIFICATION OF THE APPLICATION (Int. Cl. ³)

C 07 D 405/02
C 07 D 451/02
C 07 D 453/02
A 61 K 31/35
A 61 K 31/445

TECHNICAL FIELDS SEARCHED (Int.Cl. ³)

C 07 D 405/00
C 07 D 451/00
C 07 D 453/00

CATEGORY OF CITED DOCUMENTS

X: particularly relevant if taken alone
Y: particularly relevant if combined with another document of the same category
A: technological background
O: non-written disclosure
P: intermediate document
T: theory or principle underlying the invention
E: earlier patent document, but published on, or after the filing date
D: document cited in the application
L: document cited for other reasons

&: member of the same patent family, corresponding document

X The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
VIENNA	22-10-1982	BRUS

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